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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,049	10/21/2003	Tomohiro Kono	038779/270668	3500

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ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,049	KONO ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-5 and 7-22* is/are pending in the application.

4a) Of the above claim(s) *7-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner of Record is now **Thaian N. Ton** of Art Unit 1632.

Applicants' Amendments and Remarks, filed 1/3/07, have been entered. Claims 1, 2 and 6 are cancelled; claims 3-5,7-22 are pending; claims 3-5 are amended; 7-21 are withdrawn; claims 3-5 and 22 are under current examination.

This action is non-final.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on July 19, 2006 is acknowledged.

Claims 7-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/19/06.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

Applicants' IDS, filed 3/2/07, has been considered.

Response to Arguments

The prior rejection of claims 1 and 4-6, under 35 U.S.C. 103(a) as being unpatentable over Amano *et al.*, Bronson *et al.* and Wallace *et al.* is withdrawn in view of Applicants' amendments and/or arguments.

The prior rejection of claim 2, under 35 U.S.C. 103(a) as being unpatentable over Amano *et al.*, Bronson *et al.* and Wallace *et al.*, as applied to claims 1 and 4-6, in further view of Canatella *et al* and Canatella *et al.*, is withdrawn in view of Applicants' amendments and/or arguments.

Claim Objections

Claim 5 is objected to because of the following informalities: the claim recites "embryo stem cell", which appears to be a misspelling of "embryonic stem cell." Appropriate correction is required.

Claim 22 is objected to for the following reasons: the claim recites "A" method of claim 3, there is only one method recited in claim 3. It is suggested that the claim be amended to recite, "The method ..."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-5 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The claims are directed to methods for preparing a donor cell for nuclear transfer (NT) comprising the steps of (a) applying electrical

stimulation to donor cells comprising differentiated and undifferentiated cells; (b) reacting the electrically stimulated donor cells of step (a) with an antibody against a membrane antigen marker that is specific to undifferentiated cells to selected undifferentiated donor cells; and (c) conducting synchronous culture of the selected undifferentiated donor cells of step (b) to a metaphase stage (claim 3). In further embodiments, the donor cell is an embryonic stem cells (claim 4); the chromosomes of the donor cell are modified by genetic engineering means (claim 5); wherein the membrane antigen marker is specifically expressed in undifferentiated cells is selected from SSEA-1, CD117 (c-kit), sca-1; and CD31 (claim 22).

Breadth of the claims. The claims are broadly directed to isolating any type of undifferentiated donor from a population of undifferentiated and differentiated cells for use in nuclear transfer.

Guidance of the Specification/The Existence of Working Examples. The specification teaches methods for preparing a donor cell for nuclear transfer using electro-stimulation and a membrane antigen marker. In particular, the specification teaches that providing a pretreated embryonic stem (ES) cell, can improve the productivity of cloned animals (see p. 3, 1st ¶). The specification teaches that the cells are electrically stimulated and then reacted with an antibody against a membrane antigen marker specific to undifferentiated cells, and contemplates various markers, including SSEA-1, CD117, sca-1, and CD31 (see pages 6-7, bridging ¶). The specification teaches that this step allows for the selection of undifferentiated donor cells (see p. 7, lines 8-10).

The working examples are directed to the culturing and electro-stimulation of mouse embryonic stem cells, the synchronous culture of the embryonic stem cells and the nuclear transfer of a metaphase-synchronized ES cell with an enucleated mouse oocyte. The resultant NT unit was transferred into a surrogate mouse and analyzed at day 19.5 for the presences of a fetus. Example 1. The specification teaches the same method steps as Example 1, but without electro-stimulation, and

then selection of positive cells for a membrane surface antigen and negative cells using anti-mouse SSEA-1 (Example 2). The specification teaches that the selected cells were then subjected to NT and then the resultant NT unit was transferred into a surrogate mouse and analyzed for presence of a fetus. See Example 3. The specification teaches two comparative examples, 1) wherein no electro-stimulation was applied to the initial ES cell; 2) wherein a "differentiated ES cell" that was judged to be negative in undifferentiated cell selection was used in NT. The specification teaches that electrical stimulation produces higher numbers of pregnancies, implantation and live pups (see Table 1); and that using an undifferentiated ES cell produces higher rates of implantation and live pups than when using a differentiated ES cell (see Table 2).

State of the Art/Predictability of the Art. The claims require both the electrical stimulation of the donor cells (which comprise undifferentiated and differentiated cells), and then isolating undifferentiated cells using a membrane antigen marker that is specific to undifferentiated cells. Thus, the working examples are directed to differentiating between undifferentiated and differentiated cells utilizing a specific antigen in order to practice the claimed invention. However, the specification fails to enable the claimed invention for the following reasons: 1) the specification teaches the isolation of "differentiated" embryonic stem cells from "undifferentiated embryonic stem cells", which is not enabling, because the art does not recognize differentiated ES cells; thus, it is unclear what a differentiated ES cell encompasses, as taught by the specification; 2) the specification teaches using markers (such as SSEA-1, CD117, sca-1, and CD31), and in the working examples SSEA-1, to identify undifferentiated cells; however, these markers, in and of themselves do not uniquely identify undifferentiated cells.

ES Cell Definition. The NIH ("Stem Cells: Scientific Progress and Future Research Directions, June 2001, Chapter 2: The Embryonic Stem Cell, pages 5-10) teaches specific, art-recognized properties for ES cells. For example, ES cells are

capable of undergoing an unlimited number of symmetrical divisions without differentiation, can give rise to differentiated cell types from all three primary germ layers of the embryo. See page 5, 2nd col. This is further supported by Thomson *et al.* (PNAS, 92:7844-7848 (August 1995)), who teach the specific, art-recognized characteristics of pluripotent primate cells - that these cells remain undifferentiated in culture in continuous passage, maintain a normal karyotype, express appropriate cell markers [alkaline phosphatase, SSEA-3, SSEA-4, TRA-160-, TRA-1-81] and, when injected into SCID mice, they consistently differentiate into derivatives of all three germ layers. See *Abstract* and p. 7845-7846. Thus, the art recognizes that a requirement of an ES cell is that is undifferentiated. The specification's comparative Example 2 (see page 13) is directed to comparing a "differentiated ES cell" to an undifferentiated ES cell in methods of nuclear transfer. There is no guidance as to what this differentiated ES cell is, other than it is negative in using a membrane antigen. The specification does not specific which membrane antigen was used to determine that this differentiated ES cell was negative.

Antigens of Undifferentiated Cells. The specification teaches various markers, SSEA-1, CD117, sca-1, and CD31, to identify undifferentiated cells from differentiated cells (see page 7, lines 1-4, and claim 22). However, utilizing only one of these antigens may not be sufficient to uniquely identify and isolate undifferentiated cells from a population of differentiated and undifferentiated cells. This is because the markers contemplated by the specification are expressed in cell types other than ES cells. Furthermore, ES cells from different species express different cell surface markers to identify them as undifferentiated. For example, Pera *et al.* (J. of Cell Science, 113: 5-10, 2000) compare markers and growth properties of mouse and primate pluripotent stem cells. SSEA-1, which is specifically used in the working examples, is a marker that is expressed in mouse ES cells, but not expressed in monkey ES cells or human ES cells. See page 8, Table 1. Ling *et al.* (J. of Cell. Physiology, 171: 104-115, 1997) teach that

hematopoietic progenitor cells express sca-1 and c-kit (see Abstract and p. 106, 1st col., Immunophenotypic analysis of ES cells and embryoid bodies). Went *et al.* [J. Clin. Onco., 22(22):4514-4522] state the following, "KIT (CD117) is a transmembrane tyrosine kinase that acts as a receptor for mast cell growth factor (also known as stem cell factor or kit ligand). It belongs to the type III family of receptor kinases and can be detected in several normal cell types including hematopoietic cells, germ cells, interstitial cell of Cajal, ductal breast epithelium, mast cells, and melanocytes. Kit expression has been detected in a variety of different region of traumatic, hypoxic, or other disease state entities." See p. 4514, 1st column, 1st ¶. Anzai *et al.* (**Develop. Growth Differ.**, 41: 51-58, 1999) teach that CD31 is a marker for hematopoietic stem cells (see Abstract and p. 54, 1st ¶).

The Amount of Experimentation Necessary. With regard to Example 1 and comparative Example 1, the specification fails to provide specific guidance to show that the electrical stimulation of the ES cells produces a higher efficiency of nuclear transfer for the following reasons: Example 1 teaches using electrical stimulation of ES cells, whereas comparative Example 1 teaches that electrical stimulation was not applied to the ES cell. However, there are no steps for the selection of an undifferentiated ES cell that is used for nuclear transfer. In particular, Example 2 teaches the same initial protocol as Example 1, except that undifferentiated cells must be separated from differentiated cells using antibodies (see page 12); thus, this implies that the cell culture that results from Example 1 contains both undifferentiated and differentiated cells. Accordingly, because there is no guidance for the cell type (differentiated or undifferentiated) that is used in Example 1 and comparative Example 1, and the results provided, with regard to the electrostimulation of these cells is unclear in the context of NT.

Additionally, the specification provides no guidance with regard the definition of the term "differentiated" versus "undifferentiated" ES cells. A ES cell, by definition, is undifferentiated, as supported by the art; furthermore, an ES cell

has art-recognized characteristics, which include the expression, or lack of expression of particular markers, as well as the ability to differentiate into cells from all three germ layers. The working examples fail to enable the breadth of the claims, because they are only directed to using a known starting cell population – undifferentiated ES cells. The claims broadly encompass using a heterogeneous population of undifferentiated and differentiated cells, electrically stimulating these cells, and then isolating undifferentiated cells using a membrane antigen marker specific to undifferentiated cells. However, the various markers contemplated by the specification fail to provide specific guidance as to how to isolate an undifferentiated cell from a heterogeneous population of cells, because these markers are expressed (or not expressed) variably in different species (such as between mouse and human ES cells), as well as in different cell types (such as ES cells and hematopoietic stem cells). Furthermore, some of the specifically contemplated markers, c-kit, are expressed in normal cell types. Accordingly, one of skill in the art, given the limited teachings in the specification, would not be able to practice the claimed invention without undue experimentation, because one of skill would not be able to uniquely identify undifferentiated cells to practice the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 5 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is incomplete. The preamble of the claim is directed to a method of preparing a donor cell for nuclear transfer; however, step (c) of the claim recites

culture of undifferentiated donor cells. Thus, the method step produces multiple donor cells, whereas the preamble of the claim is directed to preparing a single donor cell. Appropriate correction is required.

Claim 5 is unclear. The claim recites that the "chromosomes of the donor cell" are modified by genetic engineering means. This is unclear, as it encompasses whole chromosome modification, such as a translocation, or loss of an entire chromosome. If Applicants intend to recite that the donor cell is genetically modified, it is suggested that Applicants' amend the claim to recite as such. This phrase is further unclear, because claim 3 recites the term "donor cell" in step (a) – which encompasses undifferentiated and differentiated donor cells, as well as in step (c) which is directed to only undifferentiated donor cells. Thus, it is unclear to which population of donor cells the genetic modification is directed.

Claim 22 recites the limitation "the membrane antigen marker that is specifically expressed in undifferentiated cells" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim. Claim 22 depends from claim 3, which recites, "the membrane antigen marker that is specific to undifferentiated cells." Thus, claim 22's recitation does not have antecedent basis in the language of claim 3. Furthermore, it is unclear what the metes and bounds are of this phrase in claim 3, in light of claim 22, because claim 22 requires the expression of the antigen marker. Appropriate correction is required.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Thaian Ton

THAIAN N. TON
PATENT EXAMINER